

⑫

EUROPEAN PATENT APPLICATION

⑳ Application number: 80304107.8

㉑ Int. Cl.³: **C 07 D 231/14, A 61 K 31/415**

㉒ Date of filing: 14.11.80

㉓ Priority: 16.11.79 JP 149103/79

㉔ Applicant: **MORISHITA PHARMACEUTICAL CO. LTD.**,
29 Doshomachi 4-chome Higashi-ku, Osaka (JP)

㉕ Date of publication of application: 27.05.81
Bulletin 81/21

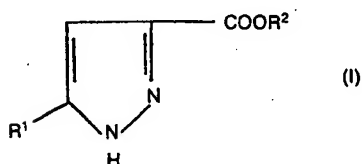
㉖ Inventor: **Seki, Kunio**, 1823-1 Ohshinohara, Yasu-cho
Yasu-gun, Shiga-ken (JP)
Inventor: **Ohki, Masahiko**, 720-77 Toba-Otsu, Yasu-cho
Yasu-gun, Shiga-ken (JP)

㉗ Designated Contracting States: **AT BE CH DE FR GB IT**
LI NL SE

㉘ Representative: **Myerscough, Philip Boyd et al, J.A. Kemp**
& Co. 14, South Square Gray's Inn, London, WC1R 5EU
(GB)

㉙ 5-Alkylpyrazol-3-carboxylic acid derivatives for use in therapy.

㉚ Derivatives of pyrazole of the general formula:



wherein R¹ represents an alkyl group of 7 to 11 carbon atoms and R² represents a hydrogen atom or a lower alkyl group, have therapeutic activity, in particular in the treatment of hyperlipemia, and have very low mammalian toxicity.

COMPLETE DOCUMENT

EP 0 029 364 A1

- 1 -

DESCRIPTION"5-ALKYLPYRAZOL-3-CARBOXYLIC ACID DERIVATIVES FOR
USE IN THERAPY"

The present invention relates to derivatives of pyrazole for use in therapy, in particular in the treatment of hyperlipemia.

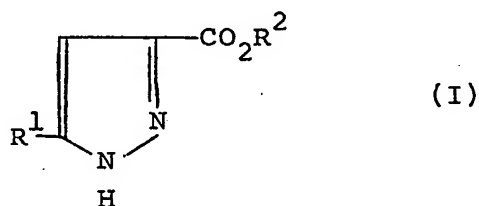
Hitherto, various antihyperlipemic
5 pharmaceutical compositions have been proposed for treatment of hyperlipemia, but they cause side effects during the long term administration to the patients. For instance, clofibrate (2-(4-chlorophenoxy)-2-methyl-
10 propanoic acid ethyl ester) which has been used as an antihyperlipemic pharmaceutical composition causes diseases in the bile duct system and is in danger of causing cancer, so that clinical administration of clofibrate has been restricted. Pharmaceutical
15 compositions containing nicotinic acid as an active ingredient for treating hyperlipemia are rarely used because of the side effect of causing flushing or eruptions on the face and skin.

5-Methylpyrazol-3-carboxylic acid was reported to reduce the level of serum lipid (refer to Kupiecki,
20 F. et al., J. pharmacol. Expt. Therap., 160 (1), 166, 1968), but it was shown later that in addition to an uncertainty as to its effectiveness in the treatment of hyperlipemia there was a side effect of causing a reduction in blood sugar-level, and accordingly it was
25 not considered suitable for use as an active ingredient in a pharmaceutical composition for treating hyperlipemia (refer to Lang, P. D. et al., *Arzneim. Forsch.*, 25 (1), 117, 1975).

After considering the present situation of
30 antilipemic agents and after synthesizing and testing

various compounds, we have found that certain derivatives of pyrazole have an excellent antilipemic activity and do not exhibit noticeable side effects.

5 The present invention thus provides a compound for use in a method of treatment of the human or animal body by therapy, wherein the compound is of the formula (I):

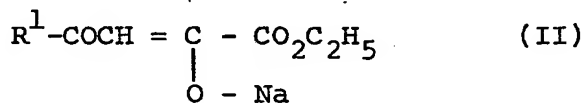


10 wherein R¹ represents an alkyl group of 7 to 11 carbon atoms and R² represents a hydrogen atom or a lower (preferably C₁ to C₄) alkyl group.

15 Although formula (I) includes within its scope known compounds (refer to Keskin et al., Istanbul University, Fen. Fak. Mecum. Setic., 34,95-108, 1969), we are aware of no disclosure concerning the pharmacological properties of the pyrazole derivatives of formula (I).

The pyrazole derivatives of formula (I) can be synthesized by the following method:

20 A sodium enolate of the general formula (II):



wherein R¹ is as defined above, which is obtainable by Claisen's condensation of higher-alkyl methyl ketone

and diethyl oxalate, is heated in a mineral acid with hydrazine hydrate under reflux for 4 to 10 hours with stirring to obtain an ethyl ester of 5-alkylpyrazole carboxylic acid.

5 In the next step, the thus obtained ester is hydrolyzed with sodium hydroxide in an aqueous lower alcoholic solution at about 100°C to obtain the 5-alkylpyrazole-3-carboxylic acid.

10 Alternatively, by heating the sodium enolate of formula (II) with hydrazine sulphate in an aqueous lower alcoholic solution of sodium hydroxide under reflux for 2 to 3 hours, 5-alkylpyrazole-3-carboxylic acids are obtained.

15 Methods for synthesizing compounds of formula (I) and their physical- and chemical properties are described in Examples 1 to 6 below. The toxicological and pharmacological properties of the compounds of these Examples will first be described as follows:

1. Toxicological property

20 Test method for acute toxicity:

Male ICR mice of body weight of 21 to 25 g were divided into several groups each consisting of 8 animals and were fasted for 17 to 18 hours and then given orally a compound of formula (I) or nicotinic acid dissolved or dispersed in an aqueous 1% carboxymethyl cellulose (CMC) solution at a rate of 0.2 ml/10 g body weight. The administered levels of each compound were 2.5 g/kg body weight and 5.0 g/kg, and from the mortalities at both levels, LD₅₀ was roughly calculated and compared with LD₅₀ of nicotinic acid.

30 The results showed that each compound of formula (I) tested had a LD₅₀ value over 5.0 g/kg body weight which was much larger than that of nicotinic acid, 4.5 g/kg.

2. Pharmacological property

Pharmacological tests were carried out on the compounds of Examples 1 to 6 using nicotinic acid as a reference.

5 (i) Pharmacological test against hypertriglyceridemia:

Seven groups of male SD rats each weighing 232 - 237 g, each group consisting of 6 animals, were used for the test animals and one group consisting of 12 animals was used as control. The test rats were made
10 to be hypertriglyceridemic by giving them an aqueous 10% by weight solution of fructose for 2 days, while the rats of the control group were given tap water.

The compounds of Examples 1 to 6 and nicotinic acid were each separately dissolved or dispersed into
15 an aqueous 1% solution of CMC at a predetermined concentration, and the thus prepared solution or dispersion was orally administered in three doses of 0.5 ml/100 g body weight, a first dose just after the commencement of the test, a second dose 24 hours after
20 the first administration, and a third dose 18 hours after the second administration. The dose of each compound was set so that each animal received 300 mg/kg of each compound as free carboxylic acid. The rats of the control group were given an aqueous 1% solution of
25 CMC only in three doses at the same intervals as the test groups. All the groups were fed with the same diet during the test period.

After 48 hours of the commencement of the test, blood samples were collected from each animal by
30 amputation of the carotid artery, and serum was separated from each blood sample and frozen to be kept until lipid analysis.

Lipid analysis:

Serum triglyceride was determined by the
35 Acetylacetone Method, and the reduction percentage of

- 5 -

lipid was calculated by the following formula:

$$\begin{aligned} & \text{amount of triglyceride in serum} \\ (1 - & \frac{\text{of test animal}}{\text{amount of triglyceride in serum}}) \times 100 \\ 5 & \text{of control} \\ & = \text{reduction percentage of lipid} \end{aligned}$$

wherein the amount for each group is the average for the test animals in the group.

Analysis for serum cholesterol:

10 The content of serum cholesterol was determined by an enzymatic method using cholesterol-oxidase, and the reduction percentage of cholesterol was calculated by the following formula:

$$\begin{aligned} 15 & (1 - \frac{\text{amount of cholesterol in serum}}{\text{of test animal}}) \times 100 \\ & \text{amount of cholesterol in serum} \\ & \text{of control} \\ & = \text{reduction percentage of cholesterol} \end{aligned}$$

20 The results of the analyses are shown in Table 1.

0029364

- 6 -

TABLE 1

Compound tested	Total Dose (mg/kg)	Reduction Percentage	
		Triglyceride (%)	Cholesterol (%)
Ethyl 5-n-heptyl-pyrazole-3-carboxylate	340	41.1	2.1
Ethyl 5-n-nonyl-pyrazole-3-carboxylate	335	63.1	29.5
Ethyl 5-n-undecyl-pyrazole-3-carboxylate	331	83.7	53.1
5-n-heptyl-pyrazole-3-carboxylic acid	300	40.6	12.5
5-n-nonyl-pyrazole-3-carboxylic acid	300	66.5	12.2
5-n-undecyl-pyrazole-3-carboxylic acid	300	69.1	40.0
nicotinic acid	300	24.1	16.4

(ii) Pharmacological test against hypercholesterolemia:

Three groups of male SD rats each weighing ca. 150g, each group consisting of five rats, were used as the test animals and one group consisting of 10 rats was used as control. All animals were fed a high cholesterol diet consisting of 1% cholesterol, 0.2% sodium cholate, 5% olive oil and commercial diet up to total 100% for 7 days.

The test compounds of the present invention and clofibrate, as a medicine for comparison, were respectively dissolved or dispersed in an aqueous 1% solution of CMC so that the volume of the solution or dispersion administered each time to each animal was 0.5 ml/100g body weight, and the solution or dispersion was orally administered once a day for 7 consecutive days so that the amount administered each time of each pyrazole derivative or of clofibrate was 200 mg/kg body weight. Water was taken ad lib. After 20 hours of fasting from the last administration, a blood sample was taken from each animal by amputation of the carotid artery and the serum separated was frozen until analysed for cholesterol as follows:

Cholesterol analysis

The content of serum cholesterol was determined by the above-mentioned method. The beta-lipoprotein-cholesterol was determined by "heparin-calcium precipitation method". The reduction percentages of cholesterol in serum and beta-lipoprotein were calculated in the same manner as above. The results are shown in Table 2.

Table 2

	Compound tested	Dose (mg/kg/day)	Reduction Percentage	
			Cholesterol in serum	Cholesterol in beta-lipoprotein
5	5-n-Nonyl-pyrazole-3-carboxylic acid	200	11.1	0.6
10	5-n-Undecyl-pyrazole-3-carboxylic acid	200	22.8	20.1
15	Clofibrate (for comparison)	200	-3.5	-2.0

As seen from Tables 1 and 2, pyrazole derivatives of formula (I) have an excellent antilipemic activity in common, which activity is superior to that of clofibrate which has been used as an antilipemic agent for a long time.

The following description is an explanation of formulating pyrazole derivatives of formula (I) into a pharmaceutical composition. In general, the pyrazole derivatives can be formulated into pharmaceutical compositions of dose unit form by known techniques. Since the pyrazole derivatives will generally be

administered orally, they are preferably formulated into tablets or capsules. When formulating the pyrazole derivatives into dose unit form, known vehicles, disintegrating agents, binding agents and lubricating agents, widely used in the pharmaceutical field, may be used.

The dose level of the pyrazole derivatives will naturally depend upon the degree of hyperlipemia, but, in general, a suitable daily oral dose is 0.2 to 3.0 g/60 kg of body weight, preferably 0.5 to 1.5 g/60 kg body weight.

The following Examples provide a detailed explanation of the synthesis (Examples 1 to 6) and the formulation (Examples 7 and 8) of pyrazole derivatives of formula (I).

Example 1

Synthesis of ethyl 5-n-heptylpyrazole-3-carboxylate:

12.6 g (0.55 mol) of metallic sodium was added slowly, with agitation, to 500 ml of absolute ethanol, until dissolved completely, and after cooling, a liquid mixture of 78 g (0.55 mol) of methyl n-heptyl ketone and 80.3 g (0.55 mol) of diethyl oxalate was slowly dropped into the solution at room temperature with agitation. Stirring was continued for 8 hours after the addition, at room temperature. The resulting yellow precipitate was collected by filtration and recrystallized from ethanol to provide sodium 1-ethoxycarbonyl-3-oxo-1-decenolate as pale yellow needle-like crystals in an amount of 117 g corresponding to a yield of 80.0%. After dissolving 26.4 g (0.10 mol) of the sodium decenolate in 23 ml of glacial acetic acid, 5.5 g (0.11 mol) of hydrazine hydrate was dropped slowly into the solution under ice cooling. After the addition of hydrazine hydrate, the mixture was heated under

reflux for 8 hours. Then, the reaction mixture was cooled and poured into iced water, and then neutralized with an aqueous saturated solution of sodium hydrogen carbonate and extracted with benzene. The benzene layer
 5 was washed with an aqueous saturated solution of sodium chloride and dried over anhydrous sodium sulphate. After distilling off the solvent under a reduced pressure, the residue was recrystallized from petroleum ether to obtain the desired product as colourless prisms
 10 in an amount of 11.5 g corresponding to a yield of 54.8% theoretical.

Elementary analysis :

found : 65.58 % C; 9.35 % H and
 11.60 % N
 15 calcd. as $C_{13}H_{22}O_2N_2$: 65.51 % C; 9.31 % H and
 11.76 % N.

Infrared absorption spectrum

$\nu_{\text{max}}^{\text{nujol}}$ 3300 to 3100 cm^{-1} (ν_{NH}) and 1718 cm^{-1} ($\nu_{\text{C=O}}$).

Mass spectrum, m/e : 238 (M^+).

20 Nuclear magnetic resonance spectrum (NMR) (in CDCl_3) δ :

0.85 (3H, t, $J = 6 \text{ Hz}$, $\text{CH}_3(\text{CH}_2)_6$)
 1.2 to 1.5 (11H, $\text{CH}_3(\text{CH}_2)_4(\text{CH}_2)_2$ and $\text{CH}_3\text{CH}_2\text{OCO}$)
 1.65 (2H, m, $\text{CH}_3(\text{CH}_2)_4 - \text{CH}_2 - \text{CH}_2$)
 2.72 (2H, t, $J = 8 \text{ Hz}$, $\text{CH}_3(\text{CH}_2)_5 - \text{CH}_2$)
 25 4.35 (2H, q, $J = 7 \text{ Hz}$, $\text{CH}_3 - \text{CH}_2 - \text{OCO}$)
 6.55 (1H, s, H in the pyrazole ring)
 11.30 (1H, br., NH which disappears by treatment with D_2O)

Example 2:

Synthesis of 5-n-heptylpyrazole-3-carboxylic acid: 20.0 g (0.084 mol) of ethyl 5-n-heptylpyrazole-3-carboxylate obtained as in Example 1 was dissolved in 81 ml of a 5 % methanolic solution of sodium hydroxide, and the solution was heated for 5 hours in a reflux condenser. After cooling the reaction mixture water was added, then methanol was distilled off under a reduced pressure, and the residue was acidified (pH of about 2) with concentrated hydrochloric acid. The deposited white precipitate was collected by filtration and recrystallized from a mixture of distilled water and methanol to obtain 5-n-heptylpyrazole-3-carboxylic acid as colourless needle-like crystals melting at 169 - 171°C in an amount of 13.3 g corresponding to a yield of 75.2 %.

Elementary analysis :

found : 62.71 % C; 8.50 % H and
13.42 % N

calcd. as $C_{11}H_{18}O_2N_2$: 62.83 % C; 8.63 % H and
13.32 % N.

Infrared absorption spectrum

ν_{\max}^{KBr} 3240 cm^{-1} (br. ν_{OH} and NH) , 3000 to 2300 cm^{-1}
(br. $\nu_{NH_2^+}$ and CO_2H) and 1700 cm^{-1} ($\nu_{C=O}$).

Mass spectrum m/e : 210 (M^+).

NMR (in d_6 -DMSO) δ :

0.87 (3H, t, J = 7 Hz, $\underline{CH_3(CH_2)_6}$)
1.2 to 1.5 (8H, br. s, $CH_3 - \underline{(CH_2)_4} - CH_2CH_2$)
1.65 (2H, m, $CH_3(CH_2)_4 - \underline{CH_2} - CH_2$)
2.61 (2H, t, J = 7 Hz, $CH_3(CH_2)_4 - CH_2 - \underline{CH_2}$)

- 12 -

6.52 (1H, s, H in the pyrazole ring)

10.65 (2H, br., NH and CO₂H which disappear by treatment with D₂O).

Example 3:

5 Synthesis of ethyl 5-n-nonylpyrazole-3-carboxylate:

 After slowly adding and dissolving 5.2 g
(0.23 mol) of metallic sodium in 300 ml of absolute
ethanol under agitation, the resulting clear solution
10 was cooled and a liquid mixture of 39 g (0.23 mol)
of methyl n-nonyl ketone and 33.6 g (0.23 mol) of
diethyl oxalate was dropped slowly into the solution
at room temperature with agitation. After the
addition was complete, the reaction mixture was heated
15 at 60°C with agitation for 5 hours. Then, the reaction
mixture was cooled with iced water, and the resulting
yellow precipitate was collected by filtration and
recrystallized from ethanol to provide sodium
1-ethoxycarbonyl-3-oxo-1-dodeccnolate as pale yellow
20 needle-like crystals in an amount of 44 g
corresponding to a yield of 65.5 %.

 26.0 g (0.09 mol) of the thus obtained
dodeccnolate was dissolved in 23 ml of glacial acetic
acid, and 5.0 g (0.10 mol) of hydrazine hydrate was
25 slowly dropped into the solution with ice cooling
and stirring. After the addition was complete, the
reaction mixture was heated under reflux for 6 hours.
Then, the reaction mixture was cooled and poured into
iced water, and was neutralized with a saturated
30 aqueous solution of sodium hydrogen carbonate and
extracted with benzene. The benzene layer was
isolated, washed with a saturated aqueous solution
of sodium chloride and dried with anhydrous sodium
sulfate. Then, the dried benzene layer was subjected to



distillation under a reduced pressure to remove the solvent, and the residue was recrystallized from n-hexane to provide ethyl 5-n-nonylpyrazole-3-carboxylate as colourless needle-like crystals melting at
 5 37 to 38°C in an amount of 14.5 g corresponding to a yield of 63.4 %.

Elementary analysis :

found : 67.92 % C; 9.80 % H and
 10.88 % N

10 Calcd. as $C_{15}H_{26}O_2N_2$: 67.63 % of C; 9.84 % H
 and 10.52 % N.

Infrared absorption spectrum

$\nu_{\text{max}}^{\text{nujol}}$ 3300 to 3100 cm^{-1} (ν_{NH}) and 1720 cm^{-1}

15 ($\nu_{\text{C=O}}$).

Mass spectrum, m/e : 266 (M^+).

NMR (in CDCl_3) δ :

0.85 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_8$)

1.2 to 1.5 (15H, $\text{CH}_3(\text{CH}_2)_6 - \text{CH}_2\text{CH}_2$ and $\text{CH}_3\text{CH}_2\text{OCO}$)

20 1.65 (2H, m, $\text{CH}_3(\text{CH}_2)_6 - \text{CH}_2 - \text{CH}_2$)

2.72 (2H, t, $J = 8$ Hz, $\text{CH}_2(\text{CH}_2)_7 - \text{CH}_2$)

4.37 (2H, q, $J = 7$ Hz, $\text{CH}_3 - \text{CH}_2 - \text{OCO}$)

6.60 (1H, s, H in the pyrazole ring)

25 12.47 (1H, br., NH which disappears by treatment
 with D_2O).

Example 4:

Synthesis of 5-n-nonylpyrazole-3-carboxylic acid:

30 In the same manner as in Example 2, 12.0 g
 (0.045 mol) of ethyl 5-n-nonylpyrazole-3-carboxylate
 obtained as in Example 3 was hydrolyzed to 5-n-

nonylpyrazole-3-carboxylic acid, which was recrystallised from a mixture of acetone and ethanol to provide colourless needle-like crystals melting at 147 to 149°C in an amount of 7.2 g corresponding to a yield of 67.3 %.

Elementary analysis :

found : 65.60 % C; 9.23 % H and 11.82 % N

calcd. as $C_{13}H_{22}O_2N_2$: 65.51 % C; 9.31 % H and 11.76 % N.

Infrared absorption spectrum

$\nu_{\text{max}}^{\text{KBr}}$ 3280 cm^{-1} (br. ν_{OH}), 3000 to 2300 cm^{-1}

(br. ν_{NH_2} +) and 1680 cm^{-1} ($\nu_{\text{C=O}}$).

Mass spectrum : m/e 238 (M^+).

NMR (in d_6 -DMSO) δ :

0.85 (3H, t, $J = 7$ Hz, $\text{CH}_3(\text{CH}_2)_8$)

1.2 to 1.5 (12H, br. s, $\text{CH}_3(\text{CH}_2)_6 - \text{CH}_2\text{CH}_2$)

1.65 (2H, m, $\text{CH}_3(\text{CH}_2)_6 - \text{CH}_2 - \text{CH}_2$)

2.61 (2H, t, $J = 7$ Hz, $\text{CH}_3(\text{CH}_2)_6 - \text{CH}_2 - \text{CH}_2$)

6.45 (1H, s, H in the pyrazole ring)

7.87 (2H, br. NH and CO_2H which disappear by treatment with D_2O).

Example 5:

Synthesis of ethyl 5-n-undecylpyrazole-3-carboxylate:

In the same manner as in Example 3, 74 g of sodium 1-ethoxycarbonyl-3-oxo-1-tetradecenolate was obtained from 5.8 g (0.25 mol) of metallic sodium, 50 g (0.25 mol) of methyl n-undecyl ketone and 36.5 g (0.25 mol) of diethyl oxalate. Then, in the same

- 15 -

manner as in Example 3, 37 g (0.11 mol) of the thus obtained sodium tetradecenolate was reacted with 6.5 g (0.13 mol) of hydrazine hydrate to provide crude ethyl 5-n-undecylpyrazole-3-carboxylate, which was
 5 recrystallized from n-hexane to provide colourless needle-like crystals melting at 39 to 40°C in an amount of 24.2 g corresponding to a yield of 71.0 %.

Elementary analysis :

found : 67.36 % C; 9.85 % H and
 10 10.79 % N

calcd. as $C_{17}H_{30}O_2N_2$: 67.63 % C; 9.84 % H and
 10.52 % N.

Infrared absorption spectrum

$\nu_{\text{max}}^{\text{nujol}}$ 3200 to 3100 cm^{-1} (ν_{NH}) and 1722 cm^{-1}
 15 ($\nu_{\text{C=O}}$).

Mass spectrum : m/e 294 (M^+).

NMR (in CDCl_3) δ :

0.90 (3H, t, J = 6 Hz, $\text{CH}_3(\text{CH}_2)_{10}$)
 1.2 to 1.6 (19H, $\text{CH}_3(\text{CH}_2)_8(\text{CH}_2)_2$ and $\text{CH}_3\text{CH}_2\text{OCO}$)
 20 1.7 (2H, m, $\text{CH}_3(\text{CH}_2)_8 - \text{CH}_2 - \text{CH}_2$)
 2.88 (2H, t, J = 8 Hz, $\text{CH}_3(\text{CH}_2)_8\text{CH}_2 - \text{CH}_2$)
 4.65 (2H, q, J = 7 Hz, $\text{CH}_3 - \text{CH}_2 - \text{OCO}$)
 6.98 (1H, s, H in the pyrazole ring)
 12.7 (1H, br., NH which disappears by treatment
 25 with D_2O).

Example 6:

Synthesis of 5-n-undecylpyrazole-3-carboxylic acid:

In the same manner as in Example 2, 10 g
 30 (0.03 mol) of ethyl 5-n-undecylpyrazole-3-carboxylate obtained as in Example 5 was hydrolysed to

- 16 -

5-n-undecylpyrazole-3-carboxylic acid, which was recrystallized from ethanol to provide colourless needle-like crystals melting at 151 to 153°C in an amount of 7.8 g corresponding to a yield of 86.3 %.

5 Elementary analysis :

found : 67.36 % C; 9.85 % H and
10.79 % N

calcd. as $C_{15}H_{26}O_2N_2$: 67.63 % C; 9.84 % H and
10.52 % N.

10 Infrared absorption spectrum

$\nu_{\text{max}}^{\text{KBr}}$ 3270 cm^{-1} (br. ν_{OH} and ν_{NH}), 3000 to 2300
 cm^{-1} (br. $\nu_{\text{NH}_2^+}$ and CO_2H) and 1710 cm^{-1} ($\nu_{\text{C=O}}$).

Mass spectrum : m/e 266 (M^+).

NMR (in d_6 -DMSO) δ :

- 15 0.85 (3H, t, $J = 7$ Hz, $\text{CH}_3(\text{CH}_2)_{10}$)
1.2 to 1.5 (16H, br. s, $\text{CH}_3(\text{CH}_2)_8 - \text{CH}_2\text{CH}_2$)
1.60 (2H, m, $\text{CH}_3(\text{CH}_2)_8 - \text{CH}_2 - \text{CH}_2$)
2.55 (2H, t, $J = 7$ Hz, $\text{CH}_3(\text{CH}_2)_8\text{CH}_2 - \text{CH}_2$)
5.20 (2H, br. NH and CO_2H which disappear by
20 treatment with D_2O)
6.31 (1H, s, H in the pyrazole ring).

Figures 1 to 6 of the accompanying drawings show the infrared absorption spectra of the pyrazole derivatives prepared in accordance with Examples 1 to
25 6, the number of each Figure corresponding to the number of the relevant Example.

Example 7:

Preparation of tablets:

A uniform mixture of 200 g of 5-n-heptyl-
30 pyrazole-3-carboxylic acid, 50 g of lactose, 20 g of

- 17 -

potato starch, 15 g of CMC and 10 g of methylcellulose was shaped into particles by introducing the mixture together with an aqueous 50 % ethanolic solution into a tumbling forming machine, and the thus obtained
5 particles were dried using a fluidizing dryer. After drying, the particles were sifted by screening machine provided with a sieve having a sieve opening of 500 microns (32 mesh Tyler standard). The particles which
10 passed through the sieve were mixed with 3 g of talc and 2 g of magnesium stearate and the mixture was pressed in a rotary tableting machine into tablets each 9 mm in diameter and 300 mg in weight.

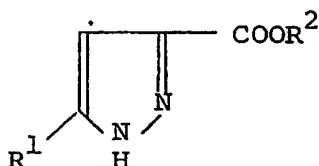
Example 8:

Preparation of capsules:

15 Particles were prepared in the same manner as in Example 7 but using 5-n-nonylpyrazole-3-carboxylic acid instead of 5-n-heptylpyrazole-3-carboxylic acid as in Example 7, and the particles were capsulated in No.1 hard capsules by using a
20 capsulating machine at a rate of 300 mg of the particles/capsule.

CLAIMS

1. A compound for use in a method of treatment of the human or animal body by therapy, characterised in that the compound is of the formula:



wherein R^1 represents an alkyl group of 7 to 11 carbon atoms and R^2 represents a hydrogen atom or a lower alkyl group.

2. A compound according to claim 1 for use in treating hyperlipemia.

3. A compound according to claim 1 or 2 wherein said compound is 5-n-heptylpyrazole-3-carboxylic acid.

4. A compound according to claim 1 or 2 wherein said compound is 5-n-nonylpyrazole-3-carboxylic acid.

5. A compound according to claim 1 or 2 wherein said compound is 5-n-undecylpyrazole-3-carboxylic acid.

6. A compound according to claim 1 or 2 wherein said compound is ethyl 5-n-heptylpyrazole-3-carboxylate.

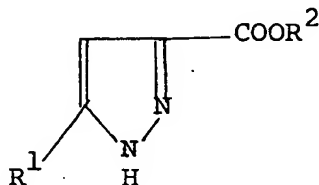
7. A compound according to claim 1 or 2 wherein said compound is ethyl 5-n-nonylpyrazole-3-carboxylate.

8. A compound according to claim 1 or 2 wherein said compound is ethyl 5-n-undecylpyrazole-3-carboxylate.

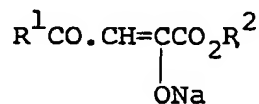
0029364

CLAIMS FOR AUSTRIA

1. A process for preparing a carboxylic acid or alkyl ester thereof of the formula:



wherein R¹ represents an alkyl group of 7 to 11 carbon atoms and R² represents a hydrogen atom or a lower alkyl group, which process is characterised by reacting a sodium enolate of the formula



wherein R¹ is as defined herein and R² is a lower alkyl group, with hydrazine hydrate or hydrazine sulphate.

2. A process according to claim 1 characterised in that an alkyl ester is prepared by reacting the sodium enolate with hydrazine hydrate by heating in a mineral acid under reflux, and if desired the alkyl ester is hydrolysed to the corresponding carboxylic acid.

3. A process according to claim 1 characterised in that a carboxylic acid is prepared by heating the sodium enolate with hydrazine sulphate in an aqueous alcoholic solution of sodium hydroxide.

FIG. 1

0029364

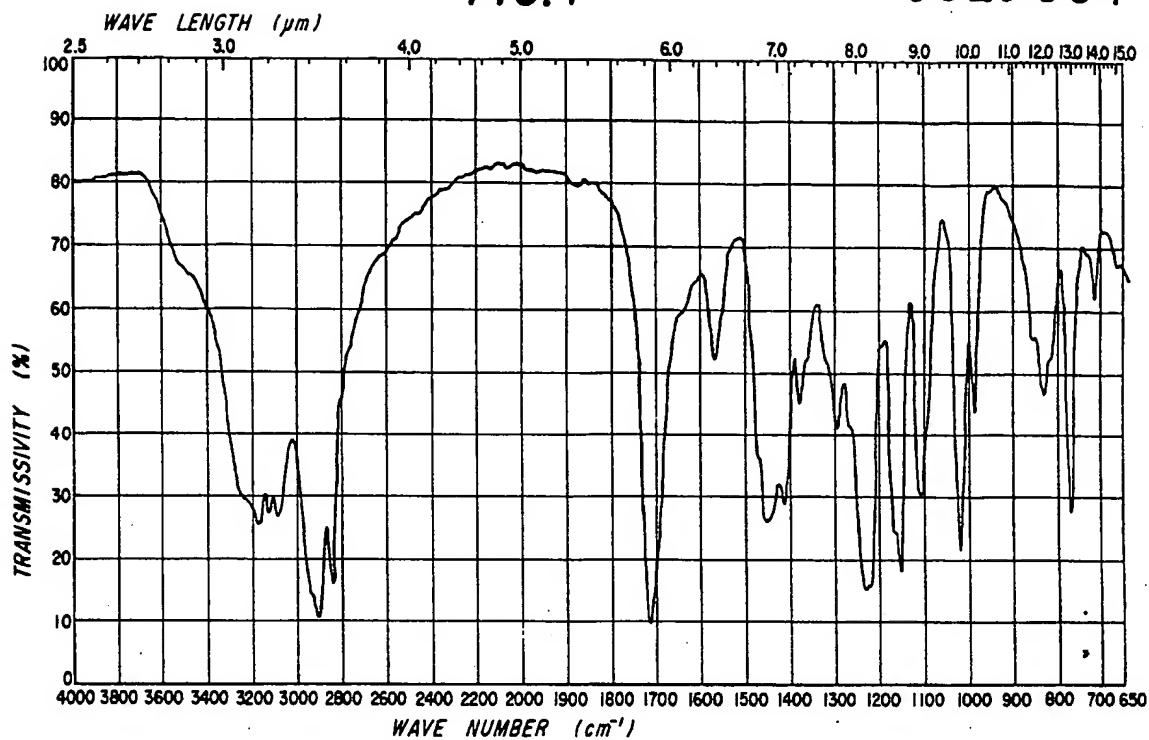


FIG. 2

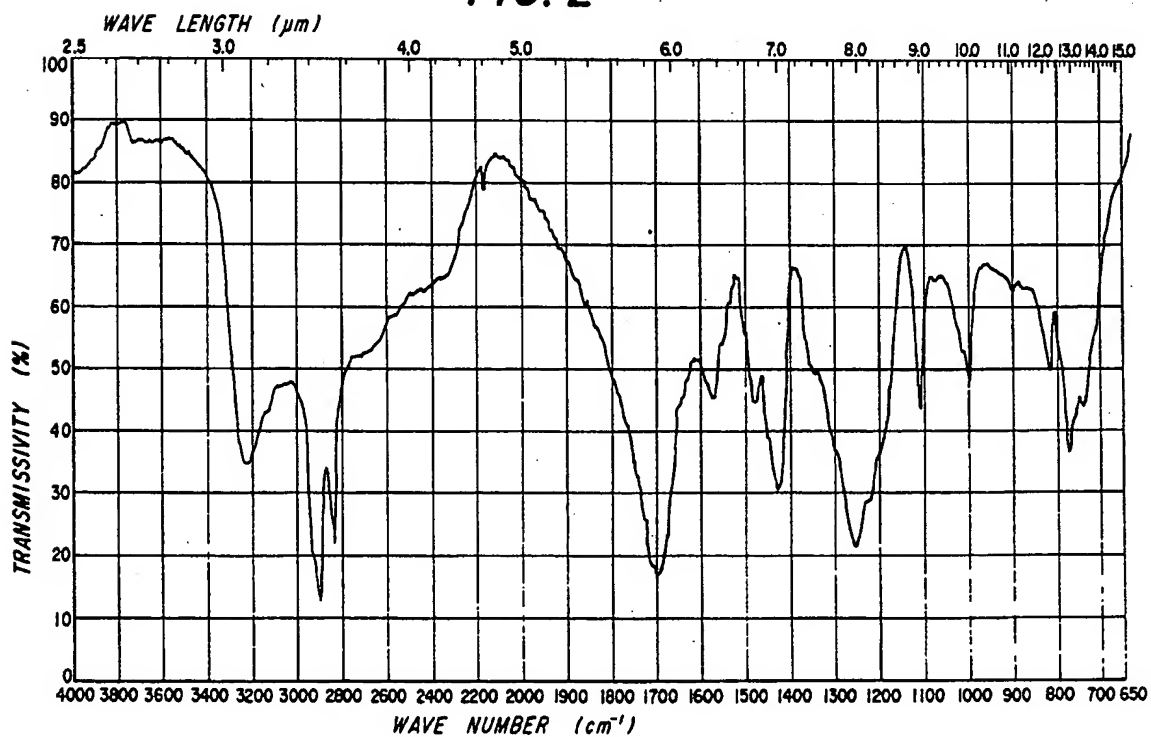


FIG. 3

0029364

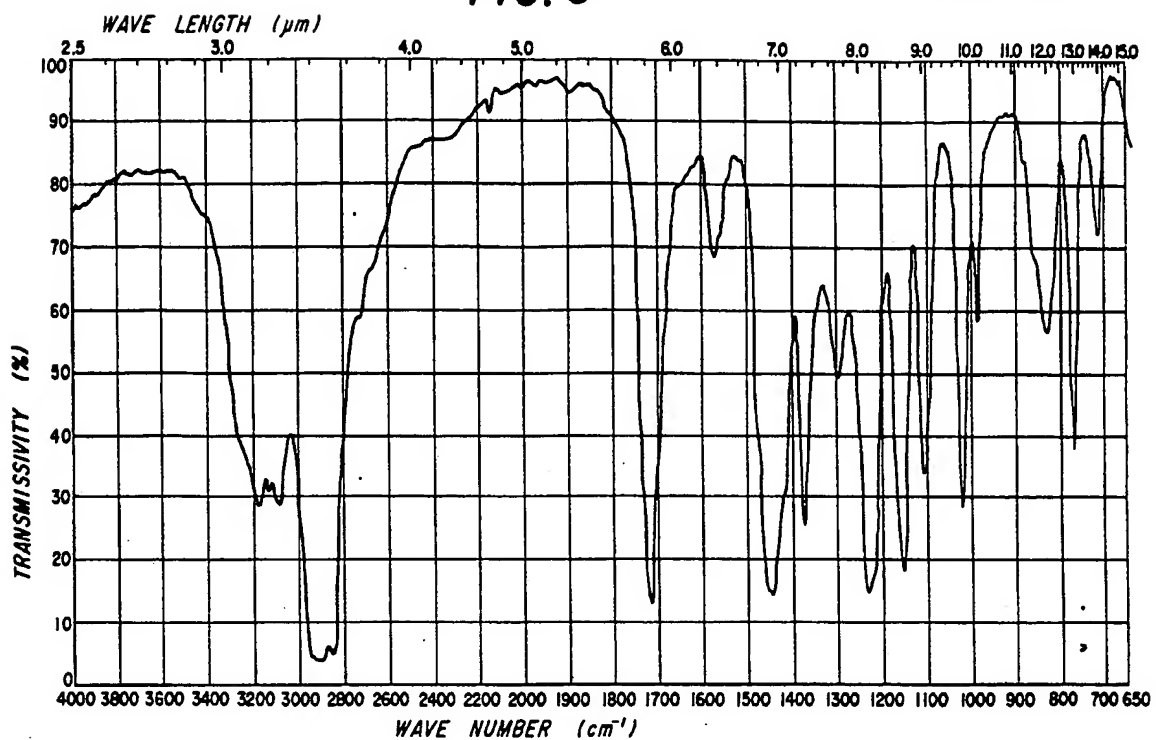


FIG. 4

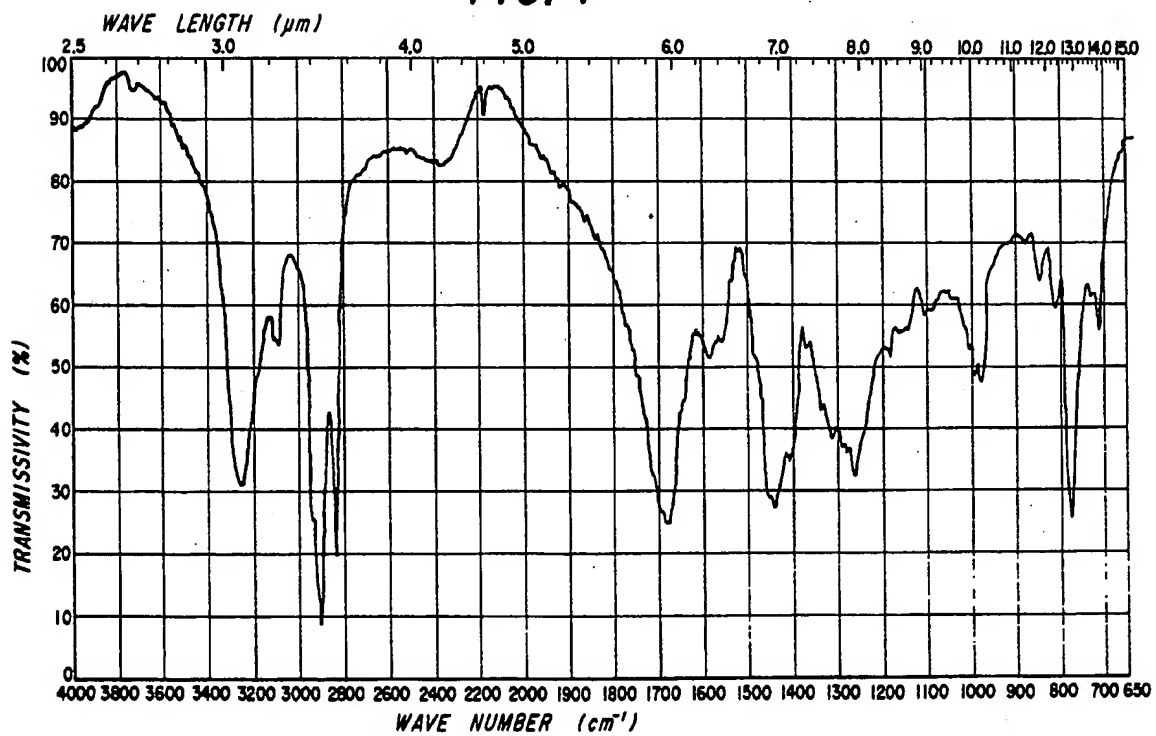


FIG. 5

0029364

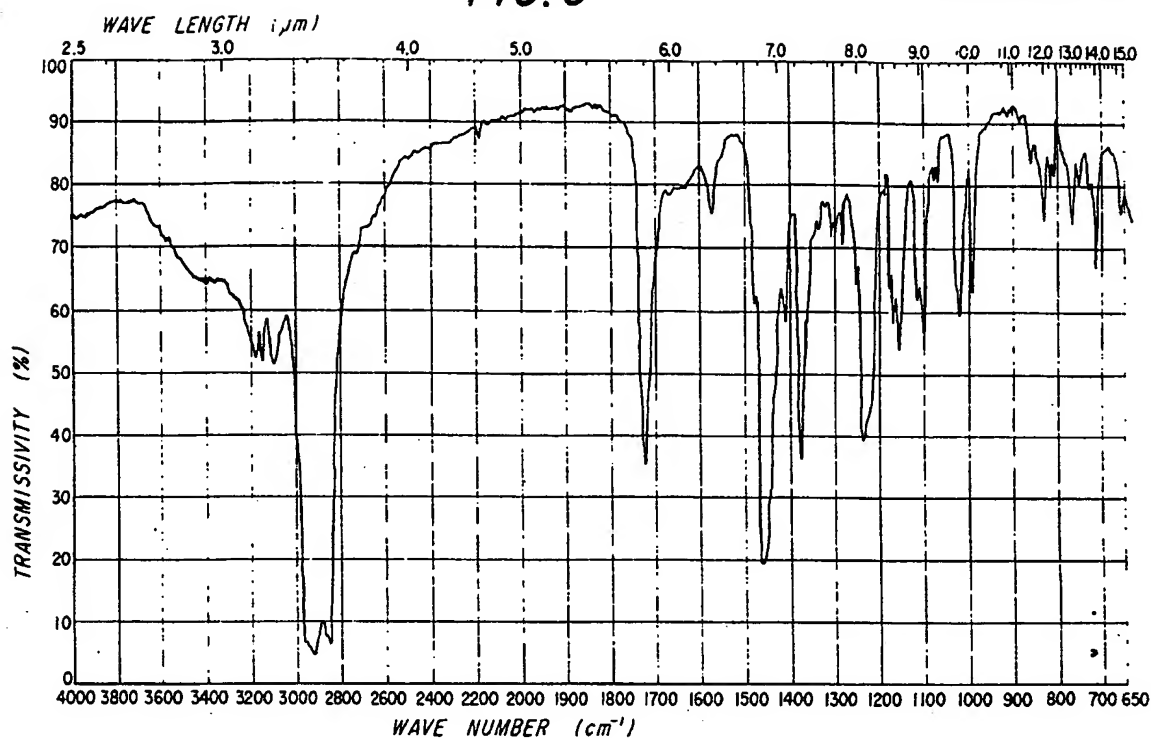
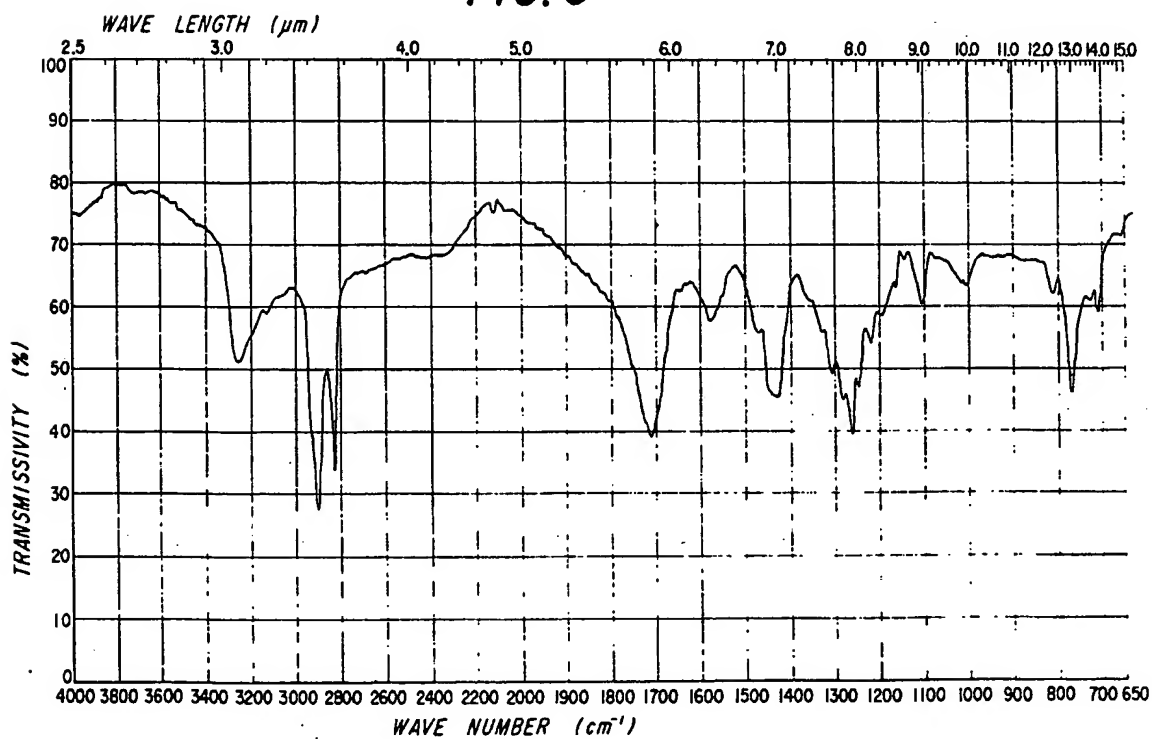


FIG. 6





European Patent
Office

EUROPEAN SEARCH REPORT

Application number

0029364.8

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	GB - A - 1 048 104 (UPJOHN) + Totality + --	1,2	C 07 D 231/14 A 61 K 31/415
	US - A - 3 449 350 (WALKER) + Abstract + --	1	
	US - A - 3 899 508 (WIKEL) + Columns 1,2 + ----	1	
			TECHNICAL FIELDS SEARCHED (Int.Cl. 3)
			C 07 D 231/00 A 61 K 31/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
X	The present search report has been drawn up for all claims		&: member of the same patent family, corresponding document
Place of search		Date of completion of the search	Examiner
VIENNA		10-02-1981	LUX